EXHIBIT B

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Processing and properties of hydroxyapatite-based biomaterials for use as hard tissue replacement implants

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This paper reviews the past, present, and future of the hydroxyapatite (HAp)-based biomaterials from the point of view of preparation of hard tissue replacement implants. Properties of the hard tissues are also described. The mechanical reliability of the pure HAp ceramics is low, therefore it cannot be used as artificial teeth or bones. For these reasons, various HAp-based composites have been fabricated, but only the HAp-coated titanium alloys have found wide application. Among the others, the microstructurally controlled HAp ceramics such as fibers/whiskers-reinforced HAp, fibrous HAp-reinforced polymers, or biomimetically fabricated HAp/collagen composites seem to be the most suitable ceramic materials for the future hard tissue replacement implants.

I. INTRODUCTION

There is a necessity for replacing bone substance which has been lost due to traumatic or nontraumatic events. The lost bone can be replaced by endogenous or exogenous bone tissues, which is connected with several problems. The use of endogenous bone substance involves additional surgery[1]; moreover, the endogenous bone is available only in limited quantities.[2] The major disadvantage of exogenous bone implants is that they may be rejected by the human body, diseases may be transmitted together with the implant,[2] also the clinical performance of exogenous bone is considerably inferior to fresh endogenous graft material.[1] For these reasons, there is a growing need for fabrication of artificial hard tissue replacement implants. The biomaterials industry worldwide has an annual turnover of $2.3 billion in the field of hard tissue repair and replacement (total of $12 billion).[3] There is currently a projected growth rate of 7–12% per annum for biomaterials in clinical applications.[3] Although the biomaterials sector is expanding, it is expected that the volume of materials required will never exceed tens of tons, as compared with thousands of tons for other developing engineering markets.[3]

Metals have been widely used for major load-bearing orthopedic applications.[4] There are, however, various problems related to metallic materials in the human body due to corrosion, wear, and/or negative tissue reaction.[5] Almost all metallic implants are encapsulated by dense fibrous tissue which prevents proper distribution of stresses and may cause loosening of the implant.[5] Therefore, several ceramic materials have been clinically applied.[4–6] Among them, ZrO_2 and Al_2O_3 exhibit high mechanical strength and good biocompatibility but, like the metals, belong to bioinert materials. [Types of implant-tissue response, after Hench[6]: if the material is toxic, the surrounding tissue dies; if the material is nontoxic and biologically inactive (bioinert), a fibrous tissue of variable thickness forms; if the material is nontoxic and biologically active (bioactive), an interfacial bond forms.] On the other hand, calcium phosphates and bioactive glasses exhibit high bioactivity and biocompatibility. (Generally speaking, biocompatibility denotes acceptance of the implant to the tissue surface. This broad term includes also nontoxicity, noncarcinogenity, chemical inertness, and stability of the material in the living body.[4] Related phenomena have been described in several reviews, for example Ref. 7 or Ref. 8.) Unfortunately, their mechanical properties are relatively poor which limits their applications to small unloaded implants, powders, coatings, and low-loaded porous implants.[6,9]

Hip-replacement prostheses made of Ti-alloy with ceramic (alumina or zirconia) heads have been widely used in the world.[5,6] About half a million such hip prostheses have been implanted and this number increases at a rate of 100,000 per year.[3] However, only in the UK, of the total 40,000 hip replacement operations performed each year, 18% are revision operations.[3] The problems are due to loosening of the implant because of its bioinertness[5] and/or stress concentration related to higher stiffness of the implant than the natural bone.[10] Therefore, there is a real need for development of "second generation"[3] of bioactive implants which promote regeneration of the surrounding tissues. Such materials could be used not only for hip-replacement prostheses but also as other artificial bones or artificial teeth roots.

Clinical success of the implant requires the simultaneous achievement of a stable interface with connective tissue and a match of the mechanical behavior of the implant with the tissue to be replaced.[6] Appropriate hard tissue replacement implants should be bioactive (i.e.,

provide a chemical bond at the bone/implant interface), have modulus equal to that of bone, and be even tougher than the bone.[11] In the case of trauma, bone should fracture rather than the implant. In contradistinction to the bone, the implant would not heal naturally and it would be very difficult to remove it from the body.[11] Moreover, if only the requirements of sufficient strength can be met, an ideal implant material should undergo biodegradation over a period of time and be replaced by the natural host tissue.[6]

Several nonmetallic materials have been proposed as candidates for artificial bones and/or teeth, but none has found wide applications. From the point of view of biocompatibility, hydroxyapatite seems to be the most suitable ceramic material for hard tissue replacement implants. Hydroxyapatite (HAp, chemical formula $Ca_{10}(PO_4)_6(OH)_2$) is the main mineral constituent of teeth and bones. HAp ceramics does not exhibit any cytoxic effects. It shows excellent biocompatibility with hard tissues and also with skin and muscle tissues.[6,9] Moreover, HAp can directly bond to the bone.[6,9] Unfortunately, due to low reliability, especially in wet environments,[6,12] the HAp ceramics cannot presently be used for heavy load-bearing applications, like artificial teeth or bones. Nevertheless, there has been a lot of research aiming to fabricate more mechanically reliable bioactive ceramics, including, of course, the HAp materials.[3,13–15]

The purpose of this paper is to review processing and properties of the HAp-based biomaterials from the point of view of preparation of hard tissue replacement implants: past achievements and current trends in this field. First, structure and properties of hard tissues (teeth and bones) are described. Then, a literature survey concerning the HAp ceramics and the HAp-based biomaterials with emphasis on preparation and properties is presented. Finally, strategies for making mechanically reliable HAp-biomaterials are discussed showing several research directions for the near future.

II. STRUCTURE AND PROPERTIES OF HARD TISSUES

It is of great importance to know the physical, chemical, and mechanical properties of the hard tissues because they provide quantitative parameters necessary for fabrication of artificial bone replacement implants. The hard tissues, i.e., bones and teeth, are, generally speaking, ceramic-organic composites with complex microstructure, as reviewed in several works.[4,16–22]

A. Structure of bone

Bone is difficult to analyze because it has so many levels of organization.[16] The main constituents of bone are collagen (20 wt.%), calcium phosphate (69 wt.%), and water (9 wt.%). Additionally, other organic materials, such as proteins, polysaccharides, and lipids are also present in small quantities.[17] Collagen, which can be considered as the matrix, is in the form of small microfibers. It is difficult to observe distinct collagen fibers because of its net-like mass appearance.[17] The diameter of the collagen microfibers varies from 100 to 2000 nm. Calcium phosphate in the form of crystallized hydroxyapatite (HAp) and/or amorphous calcium phosphate (ACP)[18] provides stiffness to the bone. The HAp crystals, present in the form of plates or needles, are about 40–60 nm long, 20 nm wide, and 1.5–5 nm thick.[4,17–19] They are deposited parallel to the collagen fibers, such that the larger dimension of crystals is along the long axis of the fiber[18] (see also Fig. 1). It is worth mentioning that the mineral phase present in the bone is not a discrete aggregation of the HAp crystals. It is rather made of a continuous phase which is evidenced by a very good strength of the bone after a complete removal of the organic phase.[4]

Mature bone exists in two main forms: compact and cancellous. Hierarchical levels of structural organization in a human compact bone (lamellar) are shown in Fig. 1. (Other kinds of compact bone, such as compact fibrous bone or compact fibrolamellar bone, will not be described here.) The mineral-containing fibers are arranged into lamellar sheets (3–7 μm thick). 4–20 lamellae, which are arranged in concentric rings around the Harversian canal, form an osteon.[4] Cross sections of the compact bone, showing cylindrical osteons (also called Harversian system) with blood vessels running along Harversian canals (in the center of each osteon) are shown in Fig. 2(a). The metabolic substances can be transported by the intercommunicating systems of canaliculi, lacunae, and Volkman's canals, which are connected with the marrow cavity.[4] The various interconnecting systems are filled with body

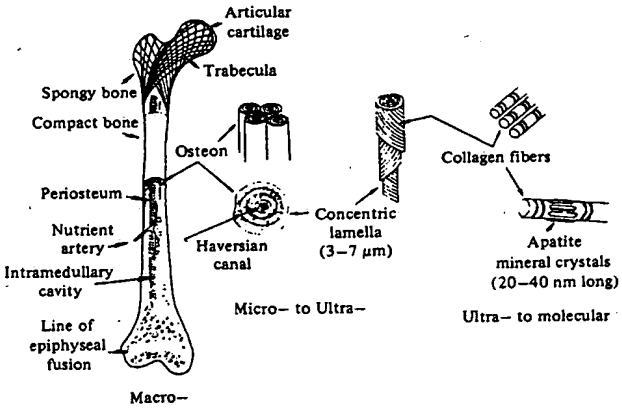

FIG. 1. Hierarchical levels of structural organization in a human long bone (after Park[4]).

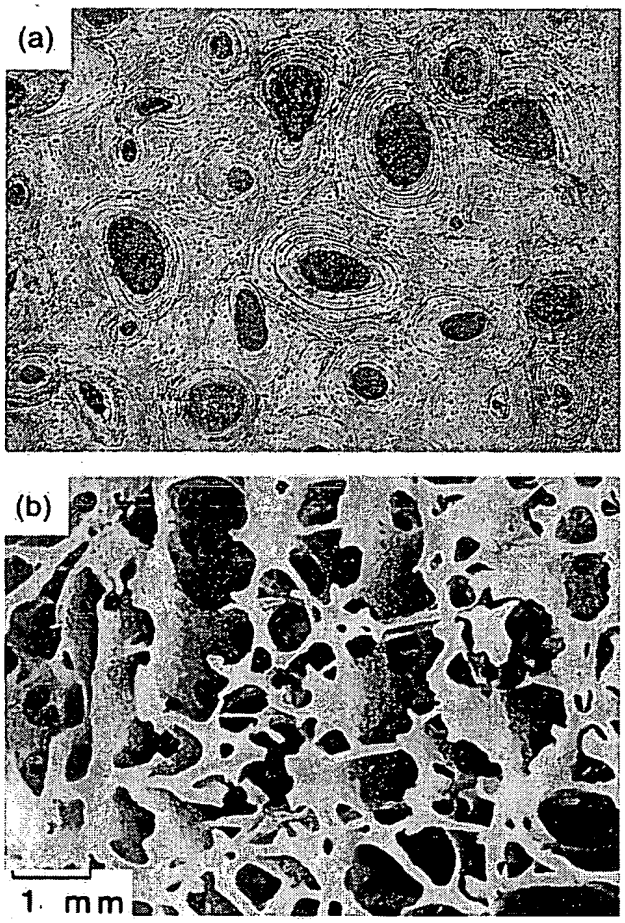

FIG. 2. (a) Optical micrograph of transverse cross section showing the microstructure of compact lamellar bone–human femora (after Katz[19]). (b) Scanning electron micrograph of plate-like cancellous bone with columnar structure (after Gibson[22]).

fluids and their volume can be as high as 19%.[4] Cancellous bone (also called trabecular or spongy bone) is a cellular material consisting of a connected network of rods or plates [Fig. 2(b)].[22] Low density, open cell, rod-like structures develop in regions of low stress while high density, closed cell, plate-like structures occur in regions of higher stress.[22]

B. Mechanical properties of bone

Organic components of bone (mainly collagen) themselves would behave as a compliant material with high toughness, low modulus, and other properties characteristic for polymers. Inorganic components, i.e., HAp crystals, provide appropriate stiffness to the bone. As a ceramic-organic composite, bone exhibits high toughness and relatively high modulus. High toughness is related not only to the presence of collagen, but also to the complicated fibrous microstructure, described in the previous section.

A representative stress-strain curve for bone (Fig. 3) shows a linear elastic region, followed by a flat plastic region at about 0.8% strain. Failure occurs at strains up to 3%.[17] It is necessary to mention that bone is a tough material at low strain rates but fractures more like a brittle material at high strain rates.[4,20] The slope of the stress-strain curve, i.e., the stiffness of the bone, increases with increasing mineral content.[17,19] Bone exhibits excellent toughness (at low strain rates!) mostly due to its hierarchical structure, which stops cracks after little propagation.[17] The main toughening mechanisms seem to be microcracks, which appear in the plastic region of the stress-strain curve,[17,18] crack deflection, and pullout effects.[20] A typical fracture surface of the bone, showing pullout of individual osteons, is presented in Fig. 4.

The mechanical properties of human compact bone are summarized in Table I. In the case of the cancellous bone, Young's modulus (measured in compression) and compressive strength are in the ranges of 1–2 GPa and 1–100 MPa, respectively.[22] With increasing bone density, both Young's modulus and compressive strength significantly increase.[22]

The mechanical properties of bone depend largely on the humidity, mode of applied load, direction of the applied load, and kind of bone. With increasing level of bone mineralization, strength increases and fracture strain decreases.[23] Moreover, strength and other mechanical properties of bone depend upon orientation of the collagen fibers,[24] bone density, and porosity,[24] and the molecular structure and arrangement of its constituent apatite crystals within their collagen matrix.[25] Finally, both strength and volume of the human bone decrease dramatically with age.[26]

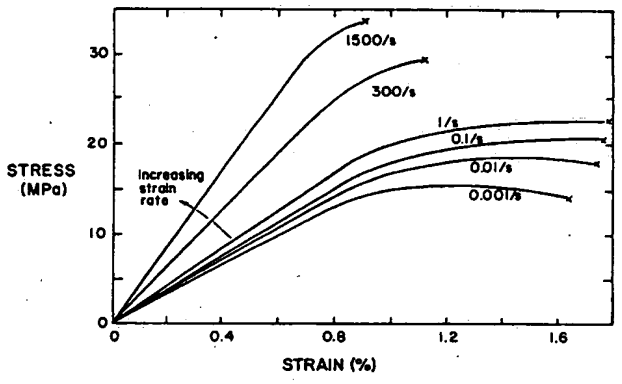

FIG. 3. A representative load-deflection curve for human compact bone (after Park[4]).

FIG. 4. A typical fracture surface of compact lamellar bone of the beef femur fractured at low strain rate (after Piekarski[20]).

C. Structure and mechanical properties of teeth

All teeth consist of two parts, the crown and the root. The root is placed in a socket called the alveolus in the maxillary (upper) or mandibular (lower) bones, being covered by a layer of cementum and attached to the bone by the periodontal membrane (a layer of fibrous connective tissue). A schematic cross section of a tooth is shown in Fig. 5.

The enamel is the hardest substance in the body and consists in 97 wt.% (92 vol.%) of relatively large HAp crystals (25 nm thick, 40–120 nm wide, 160–1000 nm long). The remaining 3 wt.% (7 vol.%) consists of organic substances and water.[21] The HAp crystals in enamel form well-defined rod- or prism-like structures about 4 μm in diameter.[21] Dentine is a mineralized tissue whose distribution of organic matrix and minerals is similar to that of regular compact bone. Dentinal tubules (3–5 μm in diameter) radiate from the pulp cavity toward the periphery and penetrate every part of the dentine.[4] Collagen fibrils (3–5 μm in diameter) fill the dentinal tubules in the longitudinal direction and the interface is cemented by a protein-polysaccharide complex substance. Pulp is a soft tissue containing thin collagenous fibers, nerve cells, blood vessels, etc.[4]

The layer of cementum surrounding the root varies from 20–50 μm at the cervix to 150–200 μm at the apex. Approximately half of the cementum is inorganic and half is composed of organic material and water.[21] The periodontal membrane is made of mostly collagenous fibers and glycoproteins (protein-polysaccharide complex).[4]

Teeth must work under stress of about 20 MPa, applied some 3000 times per day, without fatigue failures and only with moderate wear.[21] Mechanical properties of teeth are summarized in Table II.

D. Chemical composition of inorganic phases present in hard tissues

A very important point for synthesis of the HAp-based biomaterials is the chemical composition of the mineral constituents of hard tissues (teeth and bones). According to Table III, the inorganic phases present in the hard tissues contain mostly Ca^{2+} and P, considerable amounts of Na^+, Mg^{2+}, K^+, also CO_3^{2-}, F^-, Cl^-, and H_2O.[27] All these species, if applied in appropriate quantities, should be well tolerated in the implant by the surrounding tissues.

TABLE I. Mechanical properties of a compact human bone.

	Test direction related to bone axis		
	Parallel	Normal	References
Tensile strength (MPa)	124–174	49	16, 18
Compressive strength (MPa)	170–193	133	16, 18
Bending strength (MPa)	160[a]		16
Shear strength (MPa)	54		16
Young's modulus (GPa)	17.0–18.9	11.5	16, 18
	20–27 (random)		19, 481
Work of fracture (J/m^2)	6000 (low strain rate)		20, 482
	98 (high strain rate)		
K_{Ic} ($MPa \cdot m^{1/2}$)	2–12[a]		6, 482
Ultimate tensile strain	0.014–0.031	0.007	16, 18
Ultimate compressive strain	0.0185–0.026	0.028	16, 18
Yield tensile strain	0.007	0.004	18
Yield compressive strain	0.010	0.011	18

[a]Direction of measurement not specified.

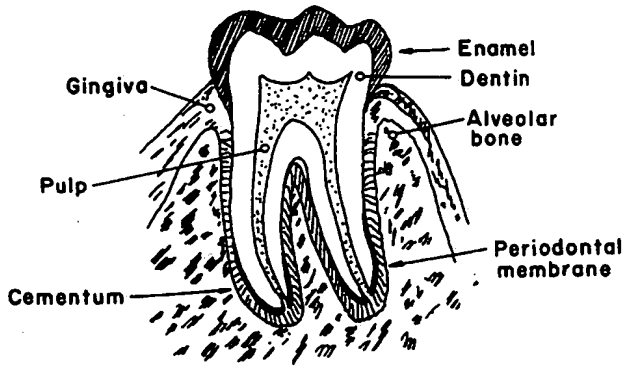

FIG. 5. Schematic diagram of a tooth (after Park[4]).

TABLE II. Mechanical properties of dentine and enamel (compiled from Ref. 21).

	Dentine	Enamel
Compressive strength (MPa)	250–350	95–370
Proportional limit in compression (MPa)	160–170	70–350
Young's modulus in compression (GPa)	11–17	9–84
Tensile strength (MPa)	21–53	10
Young's modulus in tension (GPa)	11–19	...
Flexural strength (MPa)	245–268	76
Young's modulus in bending (GPa)	12	131
Shear strength (MPa)	69–147	64–93
Proportional limit in shear (MPa)	60	...
Shear modulus (GPa)	6	...
Work of fracture (J/m^2)	200–500	13[a] 200[b]

[a]Measured parallel to prism orientation.
[b]Measured perpendicular to prism orientation.

III. HYDROXYAPATITE BIOCERAMICS–PRESENT STATUS

Hydroxyapatite (HAp) seems to be the most appropriate ceramic material for artificial teeth or bones due to excellent biocompatibility and bioactivity. Unfortunately, mechanical properties of pure HAp ceramics are poor. For example, fracture toughness (K_{Ic}) does not exceed the value of about 1.0 $MPa \cdot m^{1/2}$ (human bone: 2–12 $MPa \cdot m^{1/2}$). Additionally, the Weibull modulus (n) is low in wet environments ($n = 5–12$)[6,12] which indicates low reliability of HAp implants. Presently, the HAp ceramics cannot be used as heavy-loaded implants, such as artificial teeth or bones. Its medical applications are limited to small unloaded implants, powders, coatings, and low-loaded porous implants.[6,9] In order to improve the reliability of HAp ceramics, various reinforcements (ceramic, metallic, or polymer) have been used. Moreover, HAp-coated metals have been introduced as artificial bones or teeth. In the following sections, dense and porous HAp ceramics and HAp-based composites, will be critically reviewed with emphasis on processing, mechanical properties, biocompatibility, and (potential) medical applications. (Nonmedical applications of HAp include packing media for column chromatography, gas sensors, catalysts, and host material for lasers.[28])

A. Pure HAp ceramics

It seems that so-called pure HAp ceramics is on a plateau of development. Powder processing, forming, and densification have been understood quite well, allowing control of chemical composition and microstructures of both dense and porous HAp ceramics. The present status of the pure HAp ceramics as a biomaterial has already been well established. Any new developments concerning powder preparation/shaping/densification may affect only the price of the products but are not expected to affect their medical applications which are restricted due to the nature of HAp. This section summarizes our knowledge about processing of the HAp ceramics, starting from preparation of the HAp powders, through the fabrication of both dense and porous HAp materials, factors affecting processing, mechanical properties, biocompatibility, and finally the current applications (briefly).

1. Preparation of HAp powders

Multiple techniques have been used for preparation of HAp powders, as reviewed in several works.[9,27–32] Two main ways for preparation of HAp powders are wet methods and solid state reactions. In the case of HAp fabrication, the wet methods can be divided into three groups: precipitation,[9,27–68] hydrothermal technique,[9,29,34,43,56,68–94] and hydrolysis of other calcium phosphates.[9,34,68,95–99] Depending upon the technique, materials with various morphology, stoichiometry, and level of crystallinity can be obtained. Solid state reactions[9,32,100–103] usually give a stoichiometric and well-crystallized product, but they require relatively high temperatures and long heat-treatment times. Moreover, sinterability of such powders is usually low. In the case of precipitation, where the temperature does not exceed 100 °C, nanometric-size crystals can be prepared. They have shapes of blades, needles, rods, or equiaxed particles. Their crystallinity and Ca/P ratio depend strongly upon the preparation conditions and are in many cases lower than for well-crystallized stoichiometric hydroxyapatite. The hydrothermal technique usually gives HAp materials with a high degree of crystallinity and with a Ca/P ratio close to the stoichiometric value. Their crystal size is in the range of nanometers to millimeters. Hydrolysis of tricalcium phosphate, monetite, brushite, or octacalcium phosphate requires low temperatures (usually below 100 °C) and results in HAp needles or blades having the size of microns. However, in most

TABLE III. Comparative composition and physical properties of inorganic phases of adult human enamel, dentine, and bone (after LeGeros[27]).

	Enamel	Dentine	Bone
Composition[a]			
Calcium, Ca^{2+} [b]	36.5	35.1	34.8
Phosphorus, as P	17.7	16.9	15.2
(Ca/P) molar[b]	1.63	1.61	1.71
Sodium, Na^{+} [b]	0.5	0.6	0.9
Magnesium, Mg^{2+} [b]	0.44	1.23	0.72
Potassium, K^{+} [b]	0.08	0.05	0.03
Carbonate, as CO_3^{2-} [c]	3.5	5.6	7.4
Fluoride, F^{-} [b]	0.01	0.06	0.03
Chloride, Cl^{-} [b]	0.30	0.01	0.13
Pyrophosphate, $P_2O_7^{4-}$	0.022	0.10	0.07
Total inorganic (mineral)	97.0	70.0	65.0
Total organic[c]	1.5	20.0	25.0
Absorbed H_2O	1.5	10.0	10.0
Trace elements: Sr^{2+}, Pb^{2+}, Zn^{2+}, Cu^{2+}, Fe^{3+}, etc.			
Crystallographic properties			
Lattice parameters (±0.003 Å)			
a-axis	9.441	9.42	9.41
c-axis	6.880	6.88	6.89
Crystallinity index[f]	70–75	33–37	33–37
Crystallite size (aver.), Å	1,300 × 300	200 × 40	250 × 30
Ignition products (800 °C)	β–TCP + HAp	β–TCP + HAp	HAp + CaO

[a]Wt. %.
[b]Ashed sample.
[c]Unashed sample, IR method.
[e]Principal organic component: enamel, noncollagenous; dentine and bone, collagenous.
[f]Calculated from ratio of coherent/incoherent scattering, mineral, HAp = 100.

cases, the hydrolysis product is highly nonstoichiometric (Ca/P ratio in the range of 1.50–1.71). Another problem related to wet methods is the presence of carbonate ions and/or other impurities in the lattice of the crystallized HAp. There are also alternative techniques for preparation of HAp powders, such as sol-gel,[104–108] flux method,[9,109] electrocrystallization,[110,111] spray-pyrolysis,[112–116] freeze-drying,[117] microwave irradiation,[118] mechano-chemical method,[119] or emulsion processing.[120–122]

From the point of view of the HAp composite preparation, several very important reports concerning fabrication of HAp fibers and whiskers have appeared in the literature.[29,43,74,83–85,97,123–127] The HAp polycrystalline fibers were grown in the gel system and did not have high mechanical strength.[125,126] Preparation techniques of HAp whiskers can be divided into two main groups: (1) homogeneous precipitation method using urea[43,123,124] and (2) decomposition of chelating agents.[29,43,74,83–85,127] The first method utilizes a continuous increase of pH in the solution containing calcium and phosphate ions at high temperatures. In the case of the second method, chelating agents like EDTA, lactic acid, or citric acid are used. During the heat treatment, which is usually carried out under hydrothermal conditions, Ca complexes with chelating agents decompose, followed by the precipitation of HAp whiskers. Examples of the hydrothermally prepared HAp whiskers and HAp fine crystals are shown in Fig. 6.

2. Dense HAp ceramics

Preparation of pure, dense HAp ceramics with superior mechanical properties is possible if the starting HAp powder is stoichiometric, i.e., has Ca/P molar ratio of 1.67 (for more detailed discussion of nonstoichiometry and thermal stability of HAp, see the excellent monographs of LeGeros[27] or Elliot[30]). If the Ca/P molar ratio of the HAp exceeds the value of 1.67, CaO forms during sintering.[27,30,128,129] Existence of CaO is reported to decrease strength and may even cause decohesion of the whole material due to stresses arriving from formation of $Ca(OH)_2$ which subsequently transforms into $CaCO_3$, and related volume changes.[128,129] It may also alter the rate and extent of biodegradation.[2,130] If the Ca/P molar ratio of HAp is lower than 1.67, β– or α–tricalcium phosphate [TCP, chemical formula $Ca_3(PO_4)_2$] forms.[27,30,129,131] The presence of TCP increases slow crack growth susceptibility[132] and biodegradability of the HAp ceramics.[2,133] Moreover, the decomposition process itself may have a negative influence on the densification of

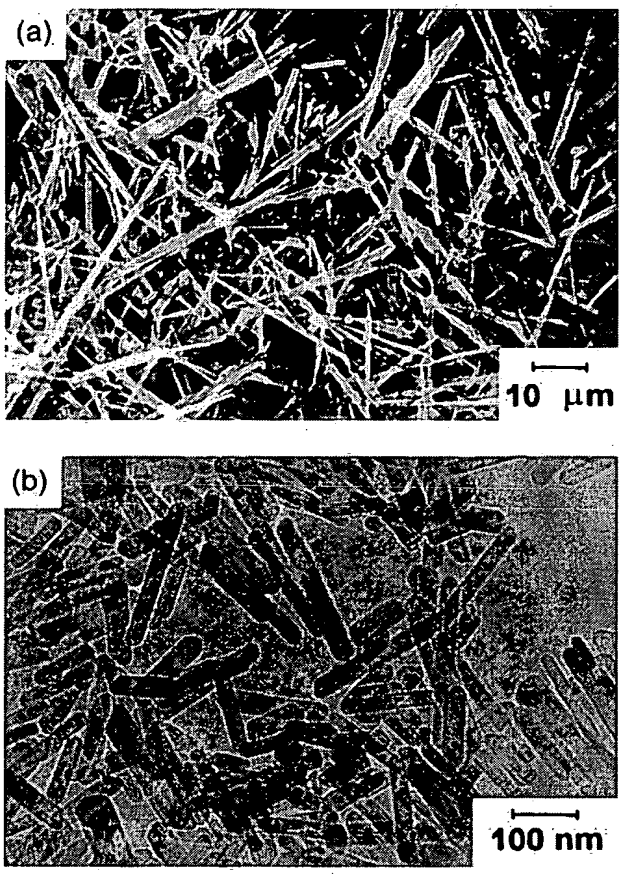

FIG. 6. Selected HAp crystals prepared hydrothermally by the authors: (a) SEM image of the HAp whiskers and (b) TEM image of the HAp fine crystals.

the HAp ceramics due to formation of a new phase and evaporation of water, decreasing in consequence the strength.[36,134] The Ca/P ratio was reported not to influence significantly the grain growth of the HAp ceramics.[135]

The decomposition temperature of HAp is a function of the partial pressure of water vapor.[28] Processing under vacuum may lead to earlier decomposition, while processing under high partial pressure of water may prevent the decomposition reaction.[136] On the other hand, the presence of water in the sintering atmosphere is reported to inhibit densification of HAp[137] and accelerate grain growth.[137,138]

It has been reported that such substitutes in HAp as fluoride (F) or chloride (Cl) do not influence either densification[139] or grain growth[140,141] of the HAp ceramics. Another very common substitute, namely carbonate ions (CO_3^{2-}), are reported to enhance sinterability of HAp ceramics if they replace only phosphate groups in the HAp lattice.[142,143] This effect is partially due to coupled substitution with Na and subsequent formation of Na, Ca-phosphates which accelerate the sintering process.[143–145] On the other hand, CO_3^{2-}-for-OH^- substitution has no effect on sintering.[143] The carbonate ions do not affect the grain growth in HAp during sintering.[141] The presence of various substitutes in HAp ceramics significantly affects its performance, not only by influencing the processing conditions, but also by changing chemical properties of the material, as discussed in detail by LeGeros.[27]

Many of the HAp powders can be pressurelessly sintered up to theoretical density at moderated temperatures (1000°–1200 °C).[9,12,44,45,52,128,134,135,146–155] Processing at higher temperatures may lead to exaggerated grain growth[12,45,153,156] and/or decomposition of HAp[30,36,157] and subsequently to strength degradation.[36,128,135,157,158] Hot pressing (HP),[9,159] hot isostatic pressing (HIP),[160–162] or HIP-postsintering[81,163] make it possible to decrease the temperature of the densification process, decrease the grain size, and achieve higher densities. This leads to finer microstructures, higher thermal stability of HAp, and subsequently better mechanical properties of the prepared HAp ceramics. An alternative technique to conventional sintering, HP, or HIP, seems to be microwave-sintering.[164–167] Forming techniques for dense HAp ceramics include in addition to common pressing, slip-casting,[168–172] tape-casting,[173,174] injection molding,[175,176] viscous plastic processing,[177] or centrifugal settling.[178]

Fracture toughness (K_{Ic}) of pure, dense HAp ceramics is in the range of 0.8–1.2 MPa·$m^{1/2}$,[12, 134, 151, 152, 154, 156, 179–189] with an average of 1.0 MPa·$m^{1/2}$. It decreases almost linearly with increasing porosity [Fig. 7(a)].[12,183,184] Fracture energy is in the range of 2.3–20 J/m^2.[180,190]

Bending strength, compressive strength, and tensile strength of the dense HAp ceramics are in the ranges of 38–250 MPa,[9,28,44,180,191] 120–900 MPa,[9,27,28,190] and 38–300 MPa,[27,28,190] respectively. The scatter of data is caused by statistical nature of strength distribution, influence of remaining microporosity, grain size, impurities etc. With increasing Ca/P ratio, strength increases, reaching the peak value around Ca/P = 1.67, and decreases suddenly when Ca/P > 1.67.[128,150] Strength decreases exponentially with increasing porosity [Fig. 7(b)].[6,28] Grain size and porosity are reported to influence the fracture path,[28] which itself has little effect on fracture toughness of HAp. Bending strength of the HAp single crystals (diameters in the range of 15–55 μm) is in the range of 200–1000 MPa.[192] The average values were 468 MPa, 361 MPa, and 501 MPa, for measurements in air, water, and simulated body fluid, respectively.[192] The presence of small amounts of carbonate ions (up to 0.7 wt. %) did not affect strength of the HAp single crystals in air, but slightly decreased it in water.[193]

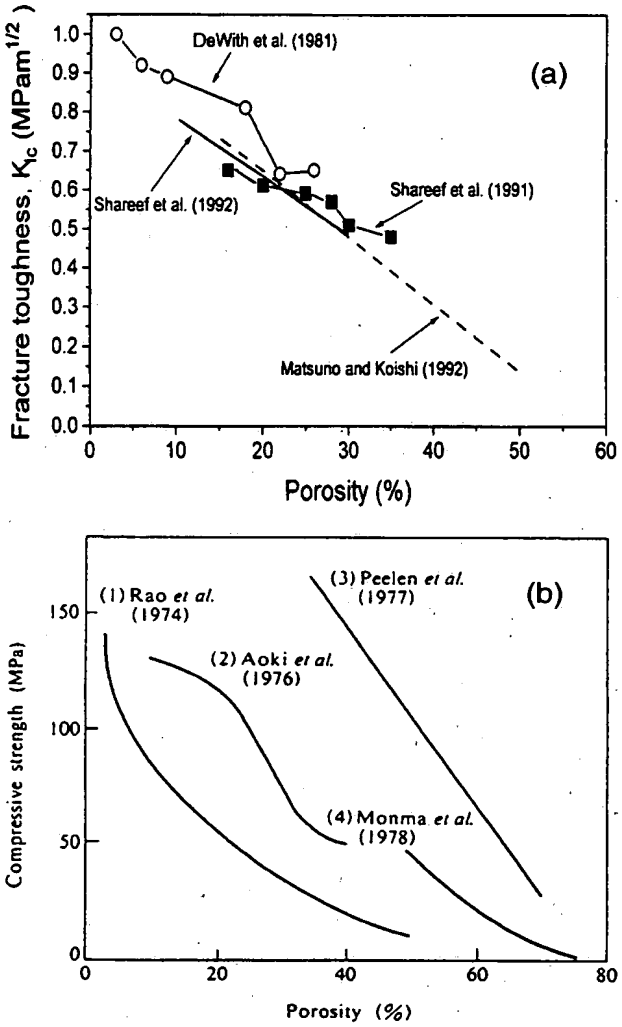

FIG. 7. Fracture toughness (a) and compressive strength (b) as a function of porosity in the HAp ceramics [(a) compiled by the authors; (b) after Yamashita and Kanazawa[28]].

Weibull modulus of the dense HAp ceramics is reported to be between 5 and 18,[12,157,194] which means that HAp behaves as a typical brittle ceramic. Slow crack growth coefficient (n) is in the range of 26–80[12,132,191] under dry condition (as compared with $n = 30$ for alumina ceramics). It drops, however, to the value of 12–49 under wet conditions,[12,132] indicating high susceptibility for slow crack growth under wet conditions. It has been suggested that grain boundaries, with Ca/P ratio lower than that of HAp, are especially susceptible to slow crack growth.[132]

Young's modulus (E) of dense HAp ceramics is in the range of 35–120 GPa. It depends mostly on measurement technique, also on remaining porosity, presence of impurities, etc. Young's modulus measured in bending is between 44 GPa and 88 GPa.[9,180] Ultrasonic techniques give higher values of about 115 GPa.[12] Vickers hardness (HV) of dense HAp is between 3.0 GPa and 7.0 GPa.[28,180] Dense HAp ceramics exhibit superplasticity at 1000°–1100 °C with a deformation mechanism based on grain boundary sliding.[195] Wear resistance and friction coefficient of the dense HAp ceramics is comparable to that of human enamel.[196]

Low values of K_{Ic} and Weibull modulus together with high susceptibility to slow crack growth (especially under wet conditions) indicate low reliability of dense HAp implants. Nevertheless, artificial teeth roots made of dense HAp were studied *in vivo* and clinically.[197–200] Attachment of gingiva to the HAp implant was comparable with the fixation of natural root cementum.[197,199] Positive bonding between the bone and the implant was also observed.[200] These effects are very important, because inadequate sealing results in excessive tooth mobility and finally their loss.[199] Unfortunately, most of the loaded dental implants were broken within 1 year from implantation due to poor mechanical properties.[197] Therefore dense HAp ceramics can be used in dentistry only as unloaded tooth root substitutes in order to maintain the volume of the residual alveolar ridge by their physical presence.[198]

Presently, one of the most important applications of dense HAp is as percutaneous devices for continuous ambulatory peritoneal dialysis, monitoring of blood pressure and blood sugar, or optical observation of inner body tissue.[6,9] It is because dense, sintered HAp exhibits excellent biocompatibility with skin tissue, much better than silicon rubber, widely used for the same purpose.[9]

3. Porous HAp ceramics

The HAp ceramics in a porous form has been widely applied as bone substitute.[6,9,201–203] Porous HAp exhibits strong bonding to the bone.[204] Moreover, the pores provide a mechanical interlock leading to a firmer fixation of the material. Bone tissue grows well into the pores, increasing strength of the HAp implant.[201–203] However, minimum pore size, required to enable ingrowth of the surrounding bone together with blood supply, is about 100 μm.[6,205] Such large pores decrease strength of the implant significantly, thus porous HAp implants cannot be heavy loaded and are used to fill only small bone defects.[6,9]

The classical way to fabricate porous HAp ceramics (pore size of 100–600 μm[205–208]) is sintering the HAp powder with appropriate pore-creating additives (for example paraffin,[209] naphthalene,[205] or hydrogen peroxide[205,209]) which evolve gases at elevated temperatures. HAp can also be cast into the $CaCO_3$ skeleton, which is then dissolved, leaving a porous network.[207]

Also worth mentioning are dense/porous layered HAp ceramics made of powders with different sinterability.[210]

Several low-temperature methods have been applied to fabricate porous HAp. Natural porous materials, like coral skeletons made of $CaCO_3$, can be converted into HAp under hydrothermal conditions (250 °C, 24–48 h) with the microstructure undamaged.[211] Porous HAp structure can also be obtained by hydrothermal hot pressing.[212–214] This technique allows solidification of the HAp powder at 100–300 °C (30 MPa, 2 h). HAp can be fabricated by mixing various calcium phosphate powders, such as $CaHPO_4 \cdot 2H_2O$, $Ca_4(PO_4)_2O$, $CaHPO_4$, $Ca_8H_2(PO_4)_6 \cdot 5H_2O$, $Ca(H_2PO_4)_2 \cdot H_2O$, α–TCP, and water. Such a procedure results in formation of HAp at 37 °C even in several minutes.[215–217,218] In another approach to low temperature synthesis of porous HAp, bicontinuous water-filled microemulsions have been used as preorganized systems for the fabrication of needle-like frameworks of crystalline HAp (2 °C, 3 weeks).[219,220]

Bending strength, compressive strength, and tensile strength of available porous HAp implants are in the ranges of 2–11 MPa,[221] 2–100 MPa,[28,208,222] and 3 MPa,[208] respectively. With increasing porosity, both strength and fracture toughness decrease dramatically (see Fig. 7). By changing the pore geometry, it is possible to control the strength of the porous HAp.[223,224] It is also worth mentioning that porous HAp ceramics is considerably less fatigue resistant than dense HAp.[225] The strength increases gradually when the bone grows into the porous network of the HAp implant.[201–203] Martin *et al.*[202] report bending strengths of 40–60 MPa for a porous implant filled with 50–60% of cortical bone. Porous HAp implants undergo biodegradation, i.e., are slowly replaced by the bone. Rate of the biodegradation is reported to be a few percent per year.[207]

Porous HAp ceramics with improved strength might be fabricated using HAp fibers or whiskers. Fibrous porous materials are known to exhibit improved strength due to interlocking of the fibers,[226] crack deflection,[227] and/or pullout.[227] Moreover, the HAp fibrous skeleton should be an appropriate reinforcement for HAp/polymer biodegradable bone substitutes.[228] There are very few reports concerning fabrication of fibrous, porous calcium phosphate ceramics. The HAp porous structures have been prepared by sintering β–$Ca(PO_3)_2$ fibers with subsequent conversion of the fibrous skeleton into HAp by treating in molten salts.[229] Fibrous porous HAp ceramics can be also prepared by sintering the HAp whiskers[230] or conversion of α–TCP under hydrothermal conditions.[214] Porous calcium phosphates with fibrous microstructure have been made by dynamic compaction of OCP and β–calcium metaphosphate fibers.[231] Unfortunately, mechanical properties have not been measured in any case.

Porous HAp ceramics has been widely used in medicine in the form of blocks or granules. The medical applications include filling bone defects,[9,205,232] drug delivery systems,[9] alveolar ridge augmentation, and orthognatic reconstruction.[207]

B. HAp-based ceramic composites

It seems that it is possible to prepare easily dense and/or porous HAp ceramics with controlled microstructure and chemical composition. This is due to a sufficient understanding of HAp processing, both during powder preparation and ceramics fabrication, as discussed in the previous section. However, there is a limit of HAp applications due to low mechanical reliability.[6,9] Preparation of HAp-based ceramic composites can partially solve the problem, as will be discussed below. Moreover, the HAp composites can be fabricated to control the biological properties of the implant (bioactivity, biodegradation etc.).

In recent years, many reinforcements, including particles,[233–235] platelets,[236] whiskers,[185,189,237,243] long fibers,[238–240] partially stabilized zirconia (PSZ),[154,187,241–244] metal dispersoids,[245–247] and nanoparticles (nanocomposites)[248] have been used in HAp ceramics to improve its reliability (see also Table IV). The highest values of fracture toughness have been achieved by DeWith and Corbijn.[238] for HAp containing 20–30% FeCralloy long metal fibers (K_{Ic} = 6.0–7.4 MPa · $m^{1/2}$, σ_f = 175–224 MPa). The question remains whether the metal-reinforced HAp composites are as biocompatible as pure HAp. No results concerning this issue have been presented in Ref. 238. In the case of other HAp-based composites K_{Ic} was in the range of 1.4–3.9 MPa · $m^{1/2}$, depending upon used reinforcement.

An advantage of the composite approach is an increase of toughness and strength of the HAp ceramics. However, the introduction of foreign materials into the HAp matrix may lead to a decrease of biocompatibility and may promote decomposition of HAp with the formation of tricalcium phosphate (TCP).[237,242,249] The presence of TCP in HAp material increases its biodegradability[2,133] and slow crack growth susceptibility.[132] Moreover, the decomposition process itself may have a negative influence on the densification of the composite due to formation of a new phase and evaporation of water, decreasing the strength in consequence. Generally speaking, bioactivity (i.e., ability of bonding to the bone) of HAp reinforced with bioinert materials should be lower than bioactivity of pure HAp.[6,250] Another undesired effect connected with most reinforcements of HAp is an increase of elastic

TABLE IV. HAp-based ceramic composites. Numbers in parentheses denote increase of strength or K_{Ic} as compared with nonreinforced HAp matrix.

Reinforcement	Relative density (%)	Flexural strength (MPa)	K_{Ic} (MPa · $m^{1/2}$)	Phase composition (calcium phosphates only)	Processing	References
5–60 vol.% whiskers (SiC, Si_3N_4, diopside)	72.5–98	180–300 (3×)	2.5–3.2 (1.8–3×)	HAp, β–TCP, α–TCP	Sintering (1250°–1300 °C), HP (1000–1200 °C) (+HIP)	185, 189, 237, 243
10–30 vol.% long metal fibers	94–100	96–224 (2×)	3.7–7.4 (6–7×)	HAp, no TCP (?)	HP (1000 °C)	238
5–30 vol.% Al_2O_3 particles	96–99.7	90–250 (1–2.5×)	1.4–2.5 (2×)	HAp, β–TCP (traces)	HP (1000°–1250 °C)	186,188,233
5–15 vol.% SiC platelets	76–81	···	···	HAp, β–TCP, α–TCP	Sintering (1000°–1200 °C)	236
5 wt.% SiC nanoparticles	···	110 (1.4×)	2.1 (1.6×)	···	···	248
10 vol.% fibers (ZrO_2, Al_2O_3, C)	68–82	···	···	HAp, β–TCP	Sintering (1000°–1150 °C)	249
10–50 vol.% (3Y)ZrO_2	93–99.5	160–310	1.0–3.0 (3×)	HAp, (β–TCP, α–TCP)	HP (1050°–1400 °C) (+HIP)	241, 242

modulus of the material. In this case the mismatch of elastic modulus between implant and bone becomes larger, therefore more load is carried by the implant. Consequently strength of the healed bone is low.[5]

As discussed earlier, the highest values of fracture toughness have been achieved for long metal fibers-reinforced HAp.[238] Unfortunately, there are multiple problems related to metallic implants due to corrosion, wear, and/or negative tissue reaction.[5] Almost all metallic implants are encapsulated by dense fibrous tissue which prevents proper distribution of stresses and may cause loosening of the implant.[5] Consequently, the biocompatibility of the HAp/metal implant is expected to be much lower than that of pure HAp ceramics.

A major advantage of ceramics as implant materials is their corrosion and wear resistance as well as minimal tissue reaction.[5] Therefore many ceramic materials, such as ZrO_2, Al_2O_3, and SiC have been used as reinforcements in HAp. The main disadvantage of HAp reinforced with partially stabilized zirconia (PSZ)[187,241–243] is degradation of zirconia in wet environments.[251–253] Transformation of the tetragonal ZrO_2 to the monoclinic phase on the surface results in formation of microcracks and consequently lowers the strength of the implant. Other HAp materials with Al_2O_3 (particles),[233–235] SiC (nanoparticles, platelets),[236,248] or cubic ZrO_2[154,241] reinforcements should be better accepted by the surrounding tissues than HAp/metal composites. However, their mechanical properties are still not satisfactory.

Significant toughening effects have been reported for whisker-reinforced HAp composites. Unfortunately many commercially available whiskers do not pass the so-called Stanton and Pott criterion and are considered as potentially carcinogenic materials. (According to Stanton *et al.*[254] and Pott,[255] the carcinogenic effect of the fibrous materials is restricted to long and thin fibers: diameter $< 1\ \mu m$, length $> 10\ \mu m$.) Additionally, erosion of HAp in the human body is reported to be even 15–30 μm per year.[206] Consequently, the reinforcing whiskers may get into the human body from the HAp matrix and cause serious health problems.

Another disadvantage of the composite approach applied to HAp is related to its processing (see Table IV). It is difficult to densify the HAp-based composites by pressureless sintering.[187,236,237] Usually more expensive techniques, such as hot pressing (HP)[186,238,241,243,256] and/or hot isostatic pressing (HIP)[187,237,242] must be used for this purpose. To overcome this problem several sintering additives, such as K-, Na-, Li-, Mg-, Ca-, and Al-fluorides,[145,257–260] K-, Li-, and Na-phosphates,[145,260,261] Li- and Na-rhenanites,[144,145] Na-, Mg-, Al-, Si-, and Li-oxides,[258,260] K-, Mg-, and Na-carbonates,[9] Ca- and K-chlorides,[145] $Na_2Si_2O_5$[145] and silicon,[262,263] have been used in HAp. Except NaF, $CaCl_2$, KCl, KH_2PO_4, $(KPO_3)_n$, $Na_2Si_2O_5$, and AlF_3, the additives enhanced densification of HAp due to liquid phase sintering[145,260–263] and/or increase of diffusion coefficients of HAp.[260] In most cases, however, decomposition of HAp with subsequent formation of TCP or CaO occurred. Presence of α– or β–TCP should be avoided, because it increases biodegradability of the HAp ceramics.[133] Existence of CaO may cause decohesion of the material due to stresses arriving from formation of $Ca(OH)_2$ and related volume changes.[128,260]

It may also alter the rate and extent of biodegradation.[130] Only MgF_2 and CaF_2 sintered with HAp at 1200 °C (1 h)[257] and Na- and Li-rhenanites[144,145] sintered with HAp at 1000 °C did not cause any decomposition (no data for NaF,[257] AlF_3,[257] and Mg-carbonates[9]). Additionally, Li- and Na-phosphates enhanced grain growth.[260,261]

Generally speaking, in spite of significantly improved strength and toughness, the HAp-based ceramic composites presented in this section did not find wide applications due to decrease of biocompatibility and/or bioactivity, difficulties with processing, and other above-mentioned problems.

Finally we should additionally mention another kind of HAp-based ceramic composites, which are fabricated not to improve mechanical reliability of HAp ceramics but to control its biological performance. These are HAp/TCP[264–268] or HAp/$CaSO_4$[269,270] composites. For example, by controlling the HAp/TCP ratio it is possible to easily control the biodegradation rate of the composite implant.[264,266]

C. HAp/bioactive glass composites

Bioactive glasses, developed by Hench almost 30 years ago, exhibit high bioactivity and biocompatibility.[6,271–287] Combination of bioactive glasses with HAp results in bioceramics with improved mechanical properties without degradation of biocompatibility and/or bioactivity.

There are several kinds of HAp/bioactive glass composites. The first one is also called bioactive glass-ceramics. In these composites, HAp and/or wollastonite or other crystalline phases crystallize from the glassy matrix during an appropriate heat treatment.[288–297] The bioactive glass-ceramics exhibits strength of 100–200 MPa, K_{Ic} of 1.0–2.6 MPa · $m^{1/2}$, fracture energy of 6–26 J/m^2, and Weibull modulus of 9.[288,290,291] Coefficient of subcritical crack growth (n) is reported to be in the range of 18–33.[290] Bioactive glass ceramics maintain high strength for a longer time than HAp, both under *in vitro* and *in vivo* conditions.[288]

HAp/bioactive glass composites can also be prepared by simple sintering of appropriate HAp/bioactive glass powder mixtures.[298–303] If the sintering is carried out below 1000 °C, HAp does not react with the bioactive glass[300,302] or this reaction is limited.[303] Reaction between HAp and bioactive glasses depends also on glass composition.

In another approach, small quantities of bioactive glass are added to HAp ceramics in order to improve densification and/or mechanical properties. Fracture toughness (K_{Ic}) of such materials is in the range of 1.3–1.7 MPa · $m^{1/2}$. Increase of strength has also been observed.[304] Usually, however, addition of bioactive glass promotes decomposition of HAp and large quantities of TCP form.[305–307]

In spite of high bioactivity, high biocompatibility, superior (but still insufficient) mechanical properties to HAp ceramics, the HAp/bioactive glass composites did not find wide application as bone substitutes. They have been used as coatings or small, unloaded implants (in middle ear surgery, percutaneous access devices, and in spinal surgery).[6,286,308]

D. HAp coatings

One of the most important clinical applications of HAp is as a coating on metal implants, such as hip joint prostheses. This concept combines mechanical advantages of metal alloys with the excellent biocompatibility, and bioactivity of HAp. Uncoated metal implants do not integrate with the bone and as bioinert materials are encapsulated by dense fibrous tissue which prevents proper distribution of stresses and may cause loosening of the implant.[5] In the case of HAp-coated metal, bone tissue integrates itself completely with the implant, even during early functional loading.[309–312]

The HAp coatings fulfill several functions. First of all, they provide stable fixation of the implant to bone[313,314] and minimize adverse reaction by provision of a biocompatible phase. Moreover, the HAp coatings decrease the release of metal ions from the implant to the body[315,316] and shield the metal surface from environmental attack. In the case of porous metal implants, the HAp coating enhances bone ingrowth into the pores.[317,318]

The plasma spraying technique[313–315,319–330] has become the most popular method to fabricate HAp coatings.[331,332] Many other methods, such as hot isostatic pressing,[332] spray-painting,[333] oxy-fuel combustion spraying,[330,334] magnetron sputtering,[335–338] flame spraying,[330] ion-beam deposition,[339] chemical deposition under hydrothermal conditions,[340–345] electrochemical deposition,[346–357] metal-organic CVD,[358] sol-gel,[359–362] pulsed laser deposition,[363–367] or electrophoresis[368,369] are also available. The coatings have been applied not only to metals, such as Ti alloys[313,314,321,340,369] or Ca–Cr–Mo alloy,[317] but also to carbon implants,[370,371] sintered ceramics like ZrO_2[372] and Al_2O_3,[359,373] and even to polymers (PMMA).[374–377]

Thickness of the HAp coatings is usually in the range of 40–200 μm.[314,316,321,346,361,363,372] With increasing thickness of the coating, concentration of metal ions released to the body decreases.[316,378] The coatings must be thick enough to resist resorbability of HAp which can be as much as 15–30 μm per year.[206] Moreover, fixation to the bone can be improved if the HAp coating has an appropriate porosity, which promotes bone ingrowth.[320] The HAp coatings should not contain impurities, such as

other calcium phosphates, amorphous calcium phosphate (ACP), or CaO, which decrease chemical stability and enhance degradation of the coatings.[346] Such phases can, however, easily be formed, if the processing is not carried out precisely enough.[335] Other problems are related to delamination of the coatings due to fatigue[9,379] and/or thermal expansion coefficient mismatch at the Ti/HAp interface.[303] To increase bonding between HAp coating and Ti substrate, an intermediate layer, consisting of bioactive glass[301,303,380] or Ca_2SiO_4[381] has been proposed.

An exciting and very promising approach is synthesis of HAp films by a biomimetic process at physiological temperature (37 °C). The films can be prepared by soaking the substrate (silica gel,[382,383] Ti,[374,384] alumina,[374] and polymers[374–377]) in the simulated body fluid (SBF). The films are uniform and dense, and their growth rate is in the range of several micrometers per day.[384]

Alternative coatings for titanium prostheses are bioactive glasses[385–387] and bioactive glass-ceramics.[386–391] The A-W-glass-ceramic coatings exhibit even higher bonding to the bone than bioactive glass coatings[386] or HAp.[388] However, there are some reports about problems with the reliability of the metal/bioactive glass coating interface.[385]

The HAp-coated hip-joint implants have been widely used. About 150,000 such implants have already been implanted in Europe, with a growing tendency.[392] The experience with high quality HAp-coated orthopedic and dental implants in the USA has been positive.[331] However, there are problems related to bone loss around the HAp-coated Ti implants due to their high stiffness.[393–395] There are also reports about degradation of the HAp coatings.[6] They have been explained by low quality of the coatings at early stages of their development.[331] Moreover, technology of HAp coatings is difficult to control[320]; thus the quality of the available HAp-coated implants may vary, depending on producer. It was recently discovered by Kokubo *et al.* that chemically treated titanium[396] and tantalum[397] are bioactive. This finding may change the well-established status of HAp coatings. Nevertheless, the titanium implants, made bioactive or with a HAp coating, are used only because better prostheses are not available at the moment.

E. HAp/polymer composites

One of the most interesting approaches to improve reliability and decrease stiffness of the HAp biomaterials is fabrication of HAp/polymer composites.

Bonfield and co-workers developed HAp/polyethylene composites.[6,398–400] With increasing HAp content, both Young's modulus and bioactivity of the composites increase, while the ductility decreases. The HAp/polyethylene composites exhibit brittle/ductile transition at a HAp volume content of 40–45%. As compared to the cortical bone, the composites have superior fracture toughness for HAp concentrations lower than 40% and similar fracture toughness in the 45–50% range. Their Young's modulus is in the range of 1–8 GPa, which is quite close to the Young's modulus of bone. Unfortunately, the HAp/polyethylene composites are not biodegradable. Moreover, the presence of bioinert polyethylene decreases the ability to bond to the bone.

There are several works concerning fabrication of HAp/collagen composites, which are similar to the bone from the point of view of chemical composition but do not have such a complex microstructure. The composites can be prepared by mixing HAp with collagen solution with subsequent hardening due to UV irradiation,[401] pressing of the HAp/collagen mixtures at 40 °C under 200 MPa for several days,[402] or precipitation of the HAp crystals on collagen fibers.[403–405] Pressing resulted in materials with very poor mechanical properties—compressive strength of 6.5 MPa and Young's modulus of 2 GPa have been achieved.[401] The most promising technique seems to be the last one. Small HAp crystals have been formed directly on the collagen fibers.[403] The HAp/collagen composite was porous and exhibited fracture energy of 510 J/m^2. In spite of still insufficient mechanical properties, the HAp/collagen mixtures exhibit higher osteoconduction than HAp or collagen alone[406] and are considered as effective fillers for large bone defects.[407,408] Another important feature of collagen-derived materials is their controlled biodegradability.[409]

Other HAp/polymer composites have also been developed.[410–419] Good examples are HAp/poly(L-lactide) composites, which have Young's modulus, compressive, bending, and tensile strengths of 5–12 GPa, 78–137 MPa, 44–280 MPa, and 10–30 MPa, respectively.[410,414] They are biodegradable and bioactive.[411,414] Unfortunately, there are several reports concerning toxicity of biodegradation products of such materials as reviewed in Ref. 420 and Ref. 421. For these and the other reasons described above, the HAp/polymer composites did not find wide applications as load-bearing implants. However, progress can be expected, especially in the case of the HAp/collagen composites, which are presently at an early stage of development, and lack an appropriate technology to fabricate bone-resembling microstructures.

F. Calcium phosphate bone cements

Finally, we would like to describe the calcium phosphate bone cements. In fact, they should be mentioned in the chapters devoted to the porous HAp and/or the HAp coatings. However, we have decided to make a separate

section for the bone cements, because it is still a rapidly developing field of research.

Generally speaking, the calcium phosphate bone cements are mixtures of various calcium phosphate powders, such as $CaHPO_4 \cdot 2H_2O$, $Ca_4(PO_4)_2O$, $CaHPO_4$, $Ca_8H_2(PO_4)_6 \cdot 5H_2O$, $Ca(H_2PO_4)_2 \cdot H_2O$, or TCP, and water or another liquid (for example, H_3PO_4 or Na_2HPO_4). The mixture transforms into HAp during setting, forming a porous body even at 37 °C.[215–218] The setting time of calcium phosphate cements can be decreased even to a few minutes.[422,423] The decay of the cements, when they get in contact with blood, can be prevented by adding sodium alginate.[424] HAp clays consisting of HAp granules in a saline solution of calcium alginate,[425,426] bioactive glass bone cements,[427] HAp-,[428] TCP-,[429] or bioactive glass-[429,430] reinforced polymeric bone cements have also been developed.

The advantages of the calcium phosphate bone cements are high biocompatibility, bioactivity,[429] and osteoconductivity.[423,425,426,429] Their serious disadvantage is relatively poor mechanical strength.[424,431] Easy shaping of the calcium phosphate bone cements enables using them to fill the bone defects much better then the HAp solid blocks, which are difficult to shape, or the HAp powders/granules, which are difficult to keep in place. The calcium phosphate bone cements may in the future replace the PMMA cements[432] as bone/implant fixation if only their mechanical properties can be improved.[430] Moreover, they can be used as fillings of the teeth root canals[433] or as drug-delivery systems.[434]

IV. CURRENT ACHIEVEMENTS AND FUTURE TRENDS IN THE FIELD OF HARD TISSUE REPLACEMENT IMPLANTS

Current needs for artificial teeth and bones as well as the mechanical properties of the hard tissues have been described in Secs. I and II. Thus the goal of the research, fabrication of artificial hard tissue replacement implants, has been well established. For the artificial bones, a material with high biocompatibility, bioactivity, and ability to biodegrade, and with mechanical properties the same (or better) than the natural bone is required. For artificial teeth roots "only" high biocompatibility and superior mechanical properties are needed. In the case of the teeth root replacements, an artificial periodontal membrane must be developed also to prevent contact of the implant surface with the alveolar bone.[435]

During evaluation of an appropriate biomaterial as a candidate for artificial hard tissue replacement implants, both mechanical and biological features must be considered. Mechanical properties of the presently available biomaterials for bone replacements are summarized in Fig. 8. In this figure, the fracture toughness has been selected as a parameter characterizing the mechanical reliability. The HAp and the HAp/bioactive glass composites are the most biocompatible among the presented biomaterials. However, K_{Ic} values of both the HAp ceramics and the HAp/bioactive glass composites are below or on the lower K_{Ic} limit of the bone, thus these materials cannot be used as heavy-load-bearing implants. The HAp-based ceramic composites are in the K_{Ic} range of the bone, and K_{Ic} of the HAp-coated titanium alloys exceed several times the upper K_{Ic} limit of the bone. However, both the HAp-based ceramic composites and the HAp-coated Ti suffer first of all too high a Young's modulus; second, there are problems related to their processing; third, their biological features are insufficient. The HAp/polymer composites have Young's modulus close to the Young's modulus of the bone and exhibit quite good mechanical reliability. Unfortunately, problems related to bioactivity decrease or toxicity of the biodegradable composites are their serious disadvantage. All these problems have already been discussed in detail in the previous sections related to the appropriate materials. Generally speaking, in the case of almost all presented bioceramic materials, with increasing mechanical reliability the biocompatibility decreases.

Fabrication of appropriate hard tissue replacement implants is a challenge for materials science for the near future. The next sections provide a survey of the recently developed apatitic and nonapatitic materials for hard tissue replacement implants. Moreover, a discussion of the processing and toughening strategies for the HAp-based biomaterials is provided, also showing directions for future research.

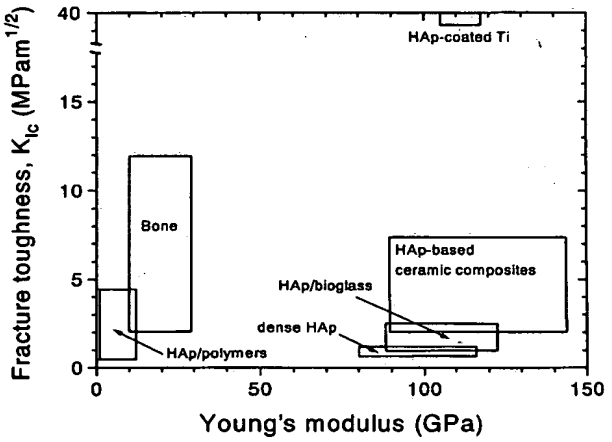

FIG. 8. Fracture toughness versus Young's modulus of the presently available biomaterials for bone replacements.

A. HAp-based biomaterials

As discussed in the previous sections, present applications of the HAp-based biomaterials, except the HAp-coated titanium alloys, include implants which must not be heavily loaded. This is due to the low reliability and slow crack growth susceptibility of the HAp ceramics. Basic approaches to achieve ceramic materials with high mechanical reliability include improved processing and/or improved toughness.[436] The improved processing strategy does not seem to work for the HAp-based ceramics, because it is difficult to control the flaw size for a long time in material exhibiting high susceptibility to subcritical crack growth. The improved toughness strategy seems to be much more promising for the HAp-based biomaterials. This is in fact a classical approach, but has not been fully exploited yet for the HAp-based materials.

The requirements for appropriate bone-replacement implants necessitate fabrication of highly reliable HAp ceramics exhibiting high strength while having pores with diameters of minimum 100 μm, to enable bone ingrowth and lower Young's modulus. For these reasons, among the available toughening strategies, the R-curve seems to be the most appropriate for the HAp ceramics. The R-curve behavior is caused by increase of fracture toughness with increasing crack (flaw) size due to shielding mechanisms acting in the crack wake.[437] In other words, a material exhibiting the R-curve becomes less flaw susceptible.[438] Therefore such reinforcements as metals, PSZ, fibers/whiskers, and/or microcracks might be applied to the HAp ceramics to improve its reliability. However, there are several limitations on usable reinforcement materials, because they must not decrease bioactivity and biocompatibility of HAp. Metals and PSZ are not appropriate materials due to bioinertness, corrosion, degradation in wet environments, difficulties with processing, etc. Microcracks are difficult to distribute uniformly in the material. Finally, only fibers/whiskers remain as possible reinforcements. Among them, long fibers such as Al_2O_3, ZrO_2, or carbon cannot be used, mostly due to processing problems (undesired thermal expansion mismatch[238] decomposition of HAp[249]) and bioinertness.[5,6] Available bioinert whiskers (SiC, Si_3N_4, etc.) must not be used in bioceramics because of their carcinogenic nature. Therefore the most promising reinforcements seem to be calcium phosphate fibers, especially the HAp whiskers or long fibers.

We should explain now, why we propose using fibers/whiskers in biomaterials. It has been widely known that application of the fibrous materials may be connected with a serious health risk due to their carcinogenic natures.[254,255,439–442] Alumina, zirconia, titania, silicon carbide, and silicon nitride are known as bioinert materials.[6] They do not dissolve easily in the human body, therefore their dimensions determine the potential health risk.[254,255] On the other hand, calcium phosphates exhibit excellent bioactivity and biocompatibility due to chemical and crystallographic similarities to the mineral constituents of bones and teeth.[27] Moreover, some of them are resorbable.[6] Among the calcium phosphates, HAp is the most biocompatible material. The accepted dissolution rate of HAp in the human body is about 15–30 μm per year.[206] As suggested by Yoshimura *et al.*,[83] in contradistinction to the other fibers and whiskers mentioned above, HAp fibrous materials should not be health hazardous due to excellent biocompatibility, bioactivity, and relatively low chemical durability.

The HAp whiskers have been already used as a *biocompatible reinforcement* in the HAp/HAp (whiskers) composites [Fig. 9(a)]. In consequence, the fracture toughness of the pure HAp ceramics has been improved even to the value of 2.0 MPa · $m^{1/2}$.[443–445] This is the highest value in the recent 25 years (Fig. 10)

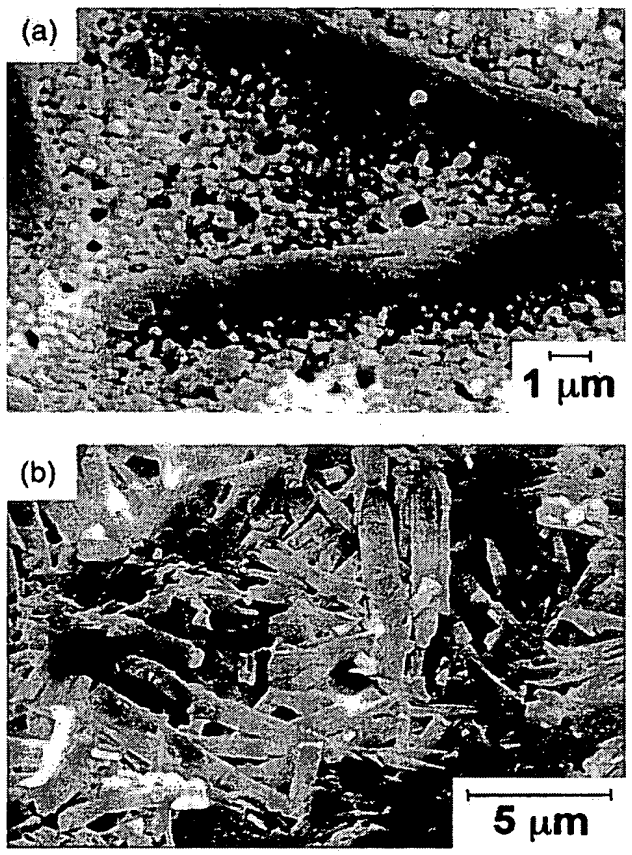

FIG. 9. SEM photographs showing selected HAp materials prepared by the authors (a) microstructure of the HAp/HAp (whiskers) composites and (b) microstructure of the fibrous-porous HAp ceramics made by sintering the HAp whiskers.

and may be improved if appropriate weak interface (biocompatible and bioactive!) will be used. The modified HAp/HAp (whiskers) composites are expected to exhibit significantly improved reliability (due to debonding with subsequent pullout and bridging[446–448]) without degradation of biocompatibility and bioactivity. β–$NaCaPO_4$ (β–rhenanite) has already been found as a weak interface for HAp[449,450] and could be applied in various microstructurally controlled HAp-based materials such as fiber-reinforced HAp, HAp laminates,[451–453] fibrous monoliths,[454] etc. However, the β–rhenanite exhibits a higher dissolution rate than HAp; thus alternative weak interface(s) should be developed.[455]

The fibrous HAp can also be used to fabricate porous HAp ceramics[230] or porous HAp/β–TCP composites,[230] as shown in Fig. 9(b). Moreover, the HAp fibrous skeleton should be an appropriate reinforcement for HAp/polymer biodegradable bone substitutes.[228] This approach seems to be very promising because it combines improved mechanical properties (fibrous reinforcements and polymers) with lowering Young's modulus of the material.

An alternative way to fabricate bone-resembling materials, i.e., the HAp/collagen composites, is biomimetics.[456,457] It combines both approaches mentioned in the beginning of this section: improved processing and improved toughness. Biomimetics is one of the most interesting and promising processing routes, being at the same time one of the most difficult ones. First of all, it requires a deep understanding of the bone formation processes. For these reasons, factors affecting assembly of the collagen fibers,[458] mineral deposition and growth of the calcium phosphates,[459–463] or collagen-HAp interactions in the bone were studied.[464,465] Bone proteins seem to control the bone formation process, but their effect has not been fully understood. Therefore, to the authors' knowledge, there are no successful studies on formation of bone materials using the biomimetic way in spite of some reports concerning preparation of HAp/collagen composites.[461]

B. Other biomaterials and approaches

There are also several other interesting approaches for fabrication of the artificial hard tissue replacement implants. For example, carbon-fiber reinforced polyetherketone composites are considered for composite hip stem development.[466,467] These materials are biocompatible,[467] and their modulus of elasticity is similar to the bone modulus of elasticity.[467] Moreover, they do not exhibit strength degradation during *in vitro* testing.[466]

Another promising candidate for total hip replacements is carbon fiber-reinforced carbon composite.[468]

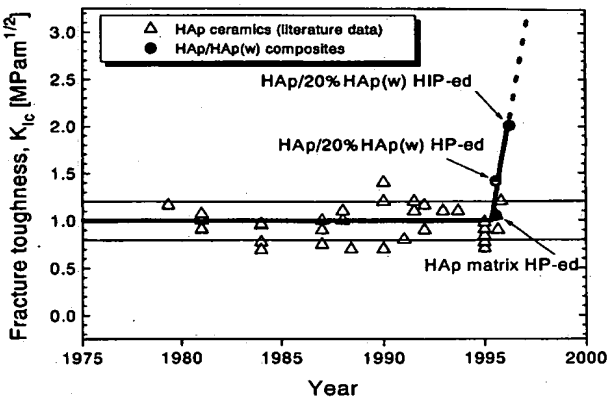

FIG. 10. Progress in toughening of the pure HAp ceramics.

Its mechanical properties are similar to those of the natural bones. Depending on the microstructure, which can be easily controlled in a wide range, fracture energy, elastic modulus, and bending strength are in the ranges of 400–2900 J/m^2, 10–72 GPa, and 100–450 MPa, respectively.[468] These mechanical properties correspond to the critical defect size of several hundreds micrometers; therefore the presence of large pores (up to 120 μm in diameter[468]) does not cause any performance limitations. Additionally, the carbon/carbon composites exhibit very high fatigue resistance.[469] The large size of the pores enables an easy ingrowth of the surrounding bone[469] and subsequently high strength of the bone/implant interface. These carbon materials are highly biocompatible[470–472]; moreover, their resorbability can be easily controlled.[469] Taking into account all these facts, the carbon/carbon composites seem to be at the moment the most promising candidates to replace traditional Ti or HAp-coated Ti prostheses.

Finally, the so-called "regeneration approach" seems to be very interesting for fabrication of the natural bone.[473] Several materials, such as biodegradable polymers,[474,475] bioactive glasses,[473,476,477] HAp/$CaSO_4$ composites,[1] bone marrow cells,[478] and bone morphogenetic proteins with some carriers like HAp, $CaSO_4$, etc.[479,480] have been used to stimulate and/or accelerate the bone regeneration. The results are very promising. Presently, this method enables regeneration of relatively small, unloaded bone defects. However, it is difficult to imagine regeneration of the whole hip joints or the extracted teeth. It seems, therefore, that research effort should be focused on fabrication of suitable artificial hard tissue replacement implants until biotechnologically grown hard tissues become available.

V. SUMMARY

The literature survey presented in this paper can be summarized as follows:

(1) There is a real need (a big, growing market) for fabrication of bioactive and possibly also resorbable hard tissue replacement implants with mechanical properties comparable to those of the natural teeth or bones.

(2) The hard tissues of humans are ceramic/organic composites (containing mostly HAp crystals and collagen fibers) with multiple levels of organization and excellent mechanical properties; thus preparation of analogous artificial materials is presently extremely difficult.

(3) Powder processing, forming, and densification of HAp have been understood quite well, allowing easy control of chemical composition and microstructures of both dense and porous HAp ceramics. Unfortunately, the mechanical reliability and slow crack growth resistance of the pure HAp ceramics is low; therefore it cannot be used as heavy-loaded implants, such as artificial teeth or bones. Its medical applications are limited to small unloaded implants, powders, coatings, and low-loaded porous implants. This status has been established for the past 10 years and there have been very little changes.

(4) Multiple HAp-based composites (HAp/ceramic, HAp/metal, and HAp/polymer) have been fabricated in order to make artificial hard tissue replacement implants, but only the HAp-coated titanium alloys have found wide application. Among the others, the most promising seem to be the HAp/collagen composites, which are presently at an early stage of development, lacking an appropriate technology to fabricate bone-resembling microstructures.

(5) From the point of view of mechanical properties and biocompatibility/bioactivity, microstructurally controlled HAp ceramics such as fibers/whiskers-reinforced HAp, fibrous HAp-reinforced polymers, or biomimetically fabricated HAp/collagen composites seem to be the most suitable ceramic materials for the future hard tissue replacement implants.

There remain also some unanswered questions. Will the carbon/carbon composites replace the titanium alloys as total hip replacements in the near future? Is it possible to make the HAp-based bioceramics applicable for the heavy-loaded implants? Is the biomimetic approach the only reasonable field of research for preparation of the artificial hard tissues? These questions, and many others, will certainly be answered only in the coming 21st century.

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